WHITE PAPER

APRECIA®
THE 3DP PHARMACEUTICAL COMPANY

REDEFINING FAST MELT FOR PHARMA:

ACHIEVING HIGH DRUG LOAD WITH RAPID DISPERSION USING 3D PRINTING

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Introduction

An online survey conducted in the United States found that 50% of surveyed American adults (N = 1002) reported difficulty swallowing tablets and capsules.[1] These numbers are even higher in pediatric and geriatric populations. Concerned that physical characteristics (e.g., size and shape) of many tablets and capsules affect patient compliance and acceptance of prescribed medication regimens, Aprecia Pharmaceuticals set out to create a convenient and easy-to-swallow dosage form. The goal was to accommodate formulation designs that could deliver higher drug loads with taste masking or a modified release profile as required. Such formulation designs are often difficult to achieve using conventional fast melt (ODTs, Thin Films) technology platforms. To accomplish this goal, Aprecia developed a commercially viable, FDA validated manufacturing process for rapidly disintegrating dosage forms that utilizes three-dimensional printing (3DP).

ZipDose® Technology

ZipDose technology is the brand name of Aprecia's 3DP manufacturing technology related to the formulation of advanced fast melt dosage forms. The name does not refer to the manufacturing process or machinery, but instead relates to the resulting formulations themselves. ZipDose technology is a platform in the sense that the formulation approach has applicability to a broad range of compounds, including both small and large molecules.

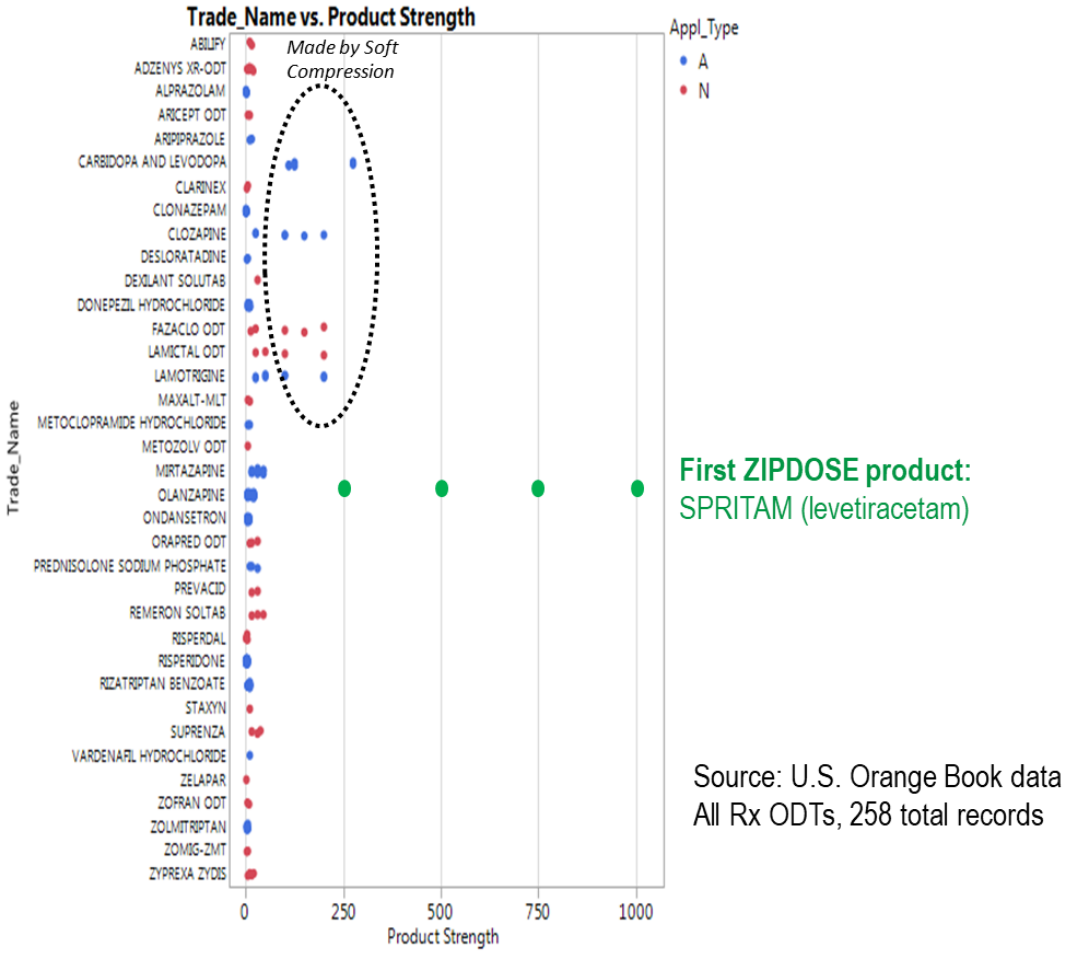
Aprecia's ZipDose technology platform combines materials science with the unique capabilities of powder liquid 3DP to formulate, develop and manufacture high dose fast melt pharmaceutical products. 3DP is the process of manufacturing a product by laying down and stitching together successive layers of a material, including API and excipients, in specifically designed patterns. This novel, flexible technology enables formulation of pharmaceutical products incorporating significantly higher amounts of API than any other fast melt technology currently available on the market, including a pharmaceutical prototype containing 1,300mg of API. ZipDose formulators have identified through careful preliminary evaluation more than 150 compounds that could be compatible with the platform. ZipDose technology is highly customizable and enables a wide range of solutions to the formulation and development of pharmaceutical products. As the ZipDose technology platform can accommodate more than one active ingredient, extended-release technologies and a broad array of taste masking capabilities, future product candidates may well offer multiple layers of product differentiation.

Existing Fast Melt Technologies

Existing orally disintegrating tablet (ODT) technologies include lyophilization (freeze-drying) and soft-compression. While ODT technologies are aimed at increasing compliance through convenience and ease of administration, this functionality has not been applied commercially to products requiring high doses of API, which typically constitute the largest, and often most difficult to swallow, tablets and

[1] OTC Company News. Hermes highlights need for better formats. http://www.hermes-pharma.com/fileadmin/data/download/Hermes_highlights_need_for_better_formats_OTCBulletin_250714.pdf. Published July 2014. Accessed July 10, 2016.

capsules. Current drug searches show no ODT products with top strengths above 275mg in the United States. Powder-liquid 3DP addresses this problem as it enables the manufacture of high dose pharmaceuticals in a fast melt dosage form.



The following table provides a comparison of currently available fast melt technologies:

Technology	Dosage Form	Highest Strength	Description	Advantages	Disadvantages
Lyophilization (Freeze-Drying)	ODT	<200mg	Drug physically trapped in a water-soluble matrix, which is then freeze dried	Highly porous product that rapidly dissolves in mouth	Lower dosage capacity as ideal drug candidate has particle size < 50 microns
Soft Compression	ODT	275mg	Direct compression tablet manufacturing that requires the inclusion of special excipients	Simplest and most cost effective manufacturing technique	Slower disintegration time due to significant loss of porosity and inclusion of special excipients
ZipDose	TOS*	1000mg	3D printed porous structure that allows for rapid dispersion and appropriate taste masking technologies	Highly porous product allowing rapid dispersion within seconds with liquid • High dose loading capabilities • Full range of taste masking options	Requires access to small amount of liquid

* TOS = Tablets, for Oral Suspension

Advantages of Power-Liquid 3DP Manufacturing for Fast Melt Technology

Rapid dispersion at high loads

Powder-liquid 3DP overcomes the limitations of existing ODT technologies to produce a high dose fast-melt pharmaceutical product that disperses in seconds with a sip of liquid. Through thoughtful selection of materials and parameters for the 3DP manufacturing process, dosage forms are designed and built with a porous structure that allows quick ingress of liquid, which then breaks the particle-to-particle connections created during the 3DP process. This loss of structure results in rapid dispersion in the mouth within seconds when taken with a sip of liquid, even at high dose loads.

Versatile taste masking

Powder-liquid 3DP enables a wide range of taste masking options, such as direct masking with sweeteners and flavors, creating chemical complexes to bind the API and using particle-level coating or encapsulation to sequester the active ingredient while it is in the mouth.

Broad application

3DP technology has significant flexibility in the range of materials it can accommodate and will have an important impact on the fast-melt pharmaceutical market. Other features may be added to complement the fast-melt functionality, such as inclusion of multiple active ingredients or extended-release of API over time.

Flexibility in product development

3DP technology offers the innovation of an automated process that does not require any molding or tooling for production, with designed placement of liquid droplets throughout the structure according to a blueprint for each strength of product. This approach enables flexibility during product development, particularly for the refinement of the product dimensions and for the degree of binding and porosity.
The following table provides a comparison of currently available fast melt technologies based on key performance criteria:

Feature	ZIPDOSE	Freeze Dried	Loosely Compressed
Dispersion Speed	1 to 15 seconds	< 3 seconds	15 to 60 seconds
Mouth Feel	Smooth	Smooth	Gritty
Dose Size	1000 mg	< 400 mg insoluble	< 500 mg
Taste Masking	Yes	Yes	Yes

Based on the information provided in the preceding table, ZipDose technology: 1) offers the combination of higher dosing with very fast dispersion, 2) is Not limited to water-insoluble APIs; and 3) can fit more material for taste-masking of difficult APIs via chemical complexation or coating / physical encapsulation.

Meeting Patient Demand: a case for ZipDose Technology

Market studies indicate that more than half of the patient population prefers ODTs to other dosage forms[2] and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%)[3]. These responses may, in part, be attributed to known ODT advantages such as ease of administration, ease of swallowing, pleasant taste, and the availability of several flavors[4]. Prior to powder-liquid 3DP manufacturing capabilities, products with an API greater than 275 mg have been unable to achieve rapid dispersion and taste mask acceptability.

Aprecia has developed commercially viable powder-liquid 3D printed ZipDose formulations to address a significant unmet patient need. ZipDose formulations should be considered any time there is a patient with swallowing difficulty, especially in the case of geriatric and pediatric patients, as a means to eliminate a possible cause for medication avoidance. In addition, patients suffering from dysphagia, motion sickness, repeated emesis and mental disorders may prefer ZipDose formulations because they cannot swallow a large quantity of water. Further, drugs exhibiting satisfactory absorption from the oral mucosa or intended for immediate pharmacological action can be advantageously formulated in ZipDose technology. Other groups that may experience problems using conventional oral dosage forms include the mentally ill, the developmentally disabled, patients who are uncooperative, on reduced liquid-intake plans, or are nauseated.

ZipDose addresses the need for medication that is easy to take and administer

Swallowing difficulties can lead to medication non-adherence. Taking medications orally, in the formulations that are currently available, works well for many people most of the time. However, liquids, tablets, and capsules can pose administration and/or swallowing challenges for patients. An online survey conducted in the United States found that 50% of surveyed American adults (N=1002)[5]reported difficulty swallowing tablets and capsules. Another survey (N=679)[6] found that of the respondents in the survey who reported swallowing difficulties, less than 25% of them discussed the problem with their healthcare provider. That same online survey found that 8% of adults with swallowing difficulties admit to skipping doses of a prescribed medication (N=679). Difficulty swallowing tablets and capsules can be a problem for many individuals and can lead to patient non-compliance with treatment regimens.

[2] K. Deepak, "Orally Disintegrating Tablets," Tablets and Capsules 7 , 30–35 (2004).

[3] D. Brown, "Orally Disintegrating Tablets: Taste Over Speed," Drug Deliv. Technol. 3 (6), 58–61 (2001).

[4] H. Seager, "Drug Delivery Products and the Zydis Fast-Dissolving Dosage form," J. Pharm. Pharmacol. 50 (4), 375–382 (1998).

[5] OTC Company News. Hermes highlights need for better formats. http://www.hermes-pharma.com/fileadmin/data/download/Hermes_highlights_need_for_better_formats_OTCBulletin_250714.pdf. Published July 2014. Accessed July 10, 2016.

[6] 40% of American adults report experiencing difficulty swallowing pills [press release]. New York, NY: PR Newswire; January 15, 2004

Dysphagia

Additionally, an estimated 16.5 million people in the US suffer from dysphagia[7], a clinically diagnosed swallowing difficulty. Dysphagia increases with age and can represent a significant challenge as it relates to the routine administration of chronic oral medications. In an effort to better understand patient profiles of those suffering from dysphagia, Aprecia funded a retrospective descriptive study using MarketScan® Commercial Claims and Medicare Supplemental databases (payer data from July 2010-June 2015) to assess the related conditions of patients with clinical dysphagia. In the overall study population with clinically diagnosed dysphagia, observations included a high rate of chronic pulmonary disease, cardiac arrhythmia, congestive heart failure, diabetes, neurological disorders, depression, psychoses and others. Data suggests there is a need for easy-to-take dosage forms within these and several therapeutic areas.

Pill Burden

The number of tablets or capsules required for the treatment of certain diseases and disorders may negatively impact patient adherence to the medication. Because ZipDose combines high dose loading with rapid dispersion it may be possible to reduce the number of pills in a medication treatment regimen. For example, if a particular regimen requires three 200mg tablets once, twice or even three times per day it may be possible to formulate one rapidly dispersing 600mg ZipDose formulation of the product. This would very likely be more acceptable to the patient and improve medication adherence.

Another approach for addressing pill burden is the formulation of fixed-dose combination products using ZipDose technology. By combining two or more APIs together in a high dose, rapid disperse, product formulation, it is possible to reduce the number of tablets or capsules the patient is required take as well as provide ease of swallowing. Lastly, ZipDose technology provides the design room to accommodate modified release technologies that makes it possible to coat APIs to achieve different release profiles. This provides yet another way to reduce patient pill burden.

Improve Current Therapies

Pharmaceutical companies and their drugs face numerous challenges in the brief window between launch and patent expiration. These challenges include earlier generic threats, increasing branded drug competition and demands for real and meaningful value from payers. To maximize products still under patent protection, companies should plan their lifecycle management (LCM) strategies well in advance of patent expiry. An earlier focus on LCM will help companies maximize product sales now and better prepare a counter-generic strategy in the future. Market enhancement strategies enable companies to increase their consumer base and add value to their existing products by developing relationships with patients and healthcare providers. As a result, market enhancement tactics help companies to earn consumer trust and maximize profits before patent expiry. For pharmaceutical companies that seek market enhancements strategies beyond the capabilities of existing fast melt technologies, ZipDose technology offers an exclusive opportunity to address patient demand.

[7] Robbins J, Langmore S, Hind JA, Erlichman M. Dysphagia research in the 21st century and beyond: proceedings from Dysphagia Experts Meeting, August 21, 2001. *J Rehabil Res Dev.* 2002;39(4):543–548.

Enhance innovation value of New Chemical Entities

The pharmaceutical industry has adopted a more patient-centric focus and is developing drugs that are more likely to be acceptable to patients and taken as intended by their doctors.[8,9] Consequently, dosing regimens, delivery methods, and product packaging are now being considered much earlier in the drug development cycle.[10] ZipDose technology can help pharmaceutical companies maximize the innovation value of new therapeutics at launch through the development of advanced dosage forms produced through a novel and patent protected 3DP manufacturing process and equipment assembly. ZipDose formulations may offer greater patient acceptance and enable market-defining functionality beyond the capabilities of conventional dosage forms.

ZipDose technology not only promises more differentiated drugs, but also helps cut the costs of drug design. Pharmaceutical chemists must conduct exhaustive tests to determine the best formulation of drugs they develop. With current solid oral dosage form manufacturing technology, pharmaceutical companies must make large numbers of tablets or capsules each with the same dose. Testing slightly different formulations becomes a lengthy and expensive task. However, with ZipDose technology, solid oral dosage forms can be made to have different formulations, so there is less waste and it takes less time to perform formulation studies. From a pharmaceutical manufacturer's point of view, this is an advantage, because the cost to develop a drug is enormous. ZipDose technology can make different formulations rapidly and the pharmaceutical company can test them for efficacy.

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Mr. Don Wetherhold brings 30 years of experience in the pharmaceutical and healthcare industry, and today serves as a key strategist and advisor to the senior executive team at Aprecia. Mr. Wetherhold previously served as the company's Chief Executive Officer (2013 – 2017) and has held numerous leadership positions across the pharmaceutical value chain throughout his career.
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[8] Miseta E. Patient-centric design: the next frontier in drug delivery. Pharmaceutical Online. March 4, 2014.
[9] Alsumidaie M. What's all this talk about patient centricity? Applied Clinical Trials. December 1, 2014.
[10] Hammeke K. New technologies in fill-finish may bring brand loyalty along with improved patient safety. Life Science Leader. April 2014.